

# CA 125 Plus Ultrasound Detects Early Ovarian Ca

BY MICHELE G. SULLIVAN

Large-scale screening for ovarian cancer with a combination of transvaginal ultrasound and cancer antigen 125 is a feasible strategy that can accurately identify early cancers, a large U.K. trial of almost 203,000 women concluded.

The combination approach carried a sensitivity of 89% and specificity of 99.8% for both primary ovarian and tubal cancers. A comparison strategy that included only transvaginal ultrasound was just as sensitive but significantly less specific, Usha Menon, Ph.D., and colleagues wrote.

Although the two methods detected similar numbers of cancers, the ultrasound-only method identified significantly more borderline ovarian tumors, resulting in almost nine times as many surgeries (845 vs. 97), wrote Dr. Menon, of the University College London, and coauthors (*Lancet Oncol.* 2009 March 10 [doi:10.1016/S1470-2045(09)70026-9]).

"This highlights an issue that has already become a significant problem in other cancer-screening strategies—the detection of cancers that may never have been diagnosed in an individual's lifetime had [the patients] not been screened," the investigators noted.

Any cancer screening trial, no matter how impressive, needs to be viewed in light of the overdiagnosis issue, said Dr. Sandra Buys of the University of Utah, Salt Lake City.

"If you have to perform 30 surgeries to cure one cancer, but a patient dies from a surgical complication, you're not really ahead in the game," she said in an in-

terview. "In this case, we have almost 950 women undergoing surgery with general anesthetic, with all its attendant risks," to find 87 cancers, 28 of which were borderline tumors. "Some of these would never have caused any health problems had they never been discovered."

The 4-year U.K. Collaborative Trial of Ovarian Cancer Screening (UKCTOCS) comprised 202,638 postmenopausal women (mean age, 60 years). They were randomized to no screening, to annual screening with transvaginal ultrasound, or to annual screening with CA 125 and transvaginal ultrasound as a second-line test.

In the multimodal screening (MMS) group, women with an abnormal CA 125 had either a repeat CA 125 in 12 weeks or an ultrasound in 6 weeks, depending on their other risk factors. On the basis of these results, they could be returned to annual screening or slated for additional testing and clinical assessment.

In the ultrasound-only screening (USS) group, women with abnormal transvaginal ultrasound findings underwent a repeat ultrasound. Depending on these results, they were returned to the screening pool, scheduled for another ultrasound, or referred for clinical assessment.

In the MMS group, 9% of women required a repeat test, and 0.2% underwent surgery. In the USS group, 12% of women required a repeat test and 2% underwent surgery, a ratio of nine surgeries in the USS group for every one in the MSS group.

Of those who underwent surgery, 834 had benign ovarian pathology or normal ovaries, with a significantly higher occurrence in the USS group compared with the MSS group (787 vs. 47). Of these women, 24 (3%) ex-

perienced a major surgical complication, with the preponderance again occurring in the USS group (22 vs. 2).

Complications included six perforations of a hollow organ, two excessive hemorrhages requiring additional surgery, one readmission for portal site pain with surgery to remove an endometriotic nodule and residual ovary, one pulmonary embolism, two deep vein thromboses, four wound dehiscences, one wound hematoma, two hernias, one significant case of ileus, one bowel obstruction, one bowel fistula, and two significant infections.

The two screening strategies detected similar numbers of ovarian or tubal malignancies (USS 45, MSS 42). But more borderline tumors were detected in the USS group (20 vs. 8). There was no significant between-group difference in the number of stage II borderline cancers.

For all primary ovarian and tubal cancers, MSS had a sensitivity of 89%, a specificity of 99.8%, and a positive predictive value of 35%. USS had a sensitivity of 75%, a specificity of 98%, and a positive predictive value of 3%. There were 19 surgeries per case of ovarian cancer in the USS group and 2 surgeries per cancer in the MSS group.

Although the study shows that women will participate in an annual prevalence screening program for ovarian cancer, it's too early to draw conclusions about either strategy's long-term effect, said Dr. Buys, an investigator in the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial. "Until we have some outcomes data, including data on mortality, we don't really know about the overdiagnosis issue. It ... gives us some important information, but as yet we can't say which of the screening techniques—or no screening at all—is better." ■

## ROMA Tool More Sensitive Than RMI to Predict Ovarian Ca

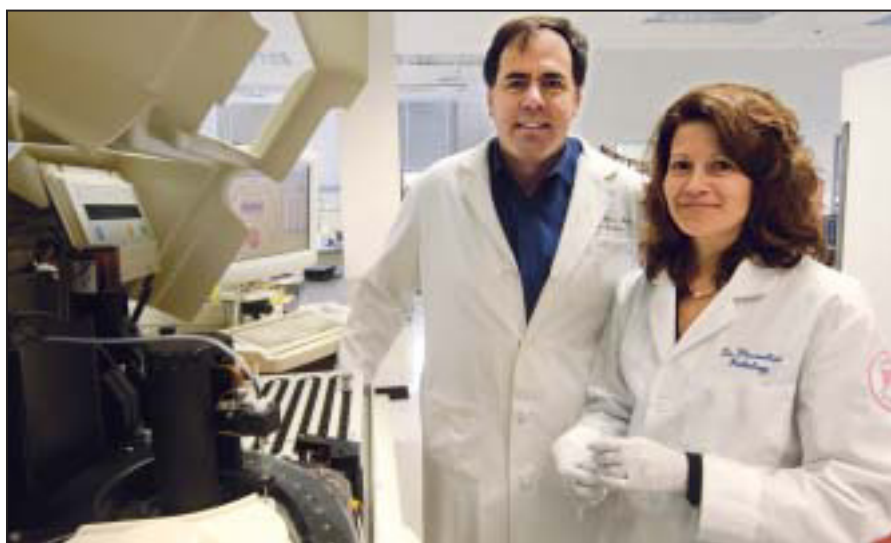
BY JANE SALODOF MACNEIL

SAN ANTONIO — A novel algorithm has been shown to be more sensitive than a widely used risk of malignancy index for predicting epithelial ovarian cancers in women who present with a pelvic mass or ovarian cyst.

The Risk of Ovarian Malignancy Algorithm (ROMA) stratifies women at high or low risk for epithelial ovarian cancer based on menopausal status and preoperative serum levels of human epididymis protein 4 (HE4) and cancer antigen 125 (CA 125). The algorithm correctly classified 94% of women with epithelial ovarian cancer in a prospective, double-blind, multicenter trial with 457 evaluable patients, researchers said (*Gynecol. Oncol.* 2009;112:40-6).

A new secondary analysis of trial data comparing patients with benign disease and all stages of epithelial ovarian cancer determined ROMA's sensitivity to be 94.3%, vs. 83.7% for the risk of malignancy index (RMI), when specificity for both was set at 75%. ROMA also was more sensitive than RMI in a comparison of patients with benign disease, tumors with a low potential for malignancy, and epithelial ovarian cancer (89% vs. 80.7%).

"This tool can be used to triage patients to physicians and centers that are experienced in the care and management of patients with ovarian cancer," Dr. Richard G. Moore said at the annual meeting of the Society of Gynecologic Oncologists. High-risk women should be referred to gynecologic oncologists and centers that



The ROMA tool correctly classified 94% of women with epithelial ovarian cancer, said Dr. Richard G. Moore, here with Dr. GERALYN MESSERLIAN.

have been shown to treat ovarian cancer with better survival outcomes and less morbidity, Dr. Moore said.

The investigators do not see ROMA as replacing the Society of Gynecologic Oncologists/American College of Obstetricians and Gynecologists referral guidelines for pelvic masses, he said, adding that they would like to see ROMA incorporated into the guidelines.

"Clinical findings and impressions are very important, but I think these markers can really help us to triage these patients," said Dr. Moore of Women and Infants Hospital and Brown University, Providence, R.I. Gynecologists now operate on fewer than half of women with ovarian cancers, he said.

The investigators compared ROMA to RMI because the latter is a validated, well-accepted tool currently in use, he said in an interview. The RMI is based on menopausal status, CA 125 levels, and ultrasound scores of 0-5.

ROMA has one formula for premenopausal and another for postmenopausal women. Both include HE4 and CA 125 levels, but the premenopausal formula weighs HE4 more heavily. "In premenopausal patients, there are many benign diseases that cause elevated CA 125, and there is no cancer," Dr. Moore said.

The algorithm was based on pooled data from a pilot study at Women and Infants Hospital and a retrospective case-control study at Massachusetts General

Hospital, Boston. The prospective trial enrolled 566 women who presented at 12 centers with pelvic masses that were documented on imaging and for which surgery was planned.

Three independent reviewers assigned an RMI score for each evaluable patient based on a preoperative ultrasound, CT, or MRI scan. Patients were included if at least two reviewers agreed on the imaging score; correlation between reviewers was 78.4%. They were blinded to tumor marker values and pathology.

The final population included 212 premenopausal and 245 postmenopausal women. All told, 123 women had epithelial ovarian cancers (80 of which were stage III), 22 had tumors with a low potential for malignancy, and 312 had benign disease.

The investigators did not report sensitivity by histology, but Dr. Moore said it was close to or at 100% in all but mucinous tumors. ROMA was much less sensitive in mucinous tumors, identifying only about half of them, he said.

Although ROMA was significantly more sensitive in other comparisons based on tumor stage, Dr. Moore did not report benign vs. stage I results because only 17 patients were stage I. Even with such small numbers, the comparison trended in favor of ROMA, he said.

The prospective trial was supported by Fujirebio Diagnostics Inc. and grants from the National Cancer Institute. Seven authors, including Dr. Moore, served as consultants to and were on the scientific advisory board for Fujirebio. ■